REMARKS

Claims 2-3, 5-21, 23-30, 37 and 118-124 were pending in the present application. Claim 121 has been cancelled. Claims 5, 17, 19, 30 and 37 have been amended. Claim 125 has been added. Accordingly, Claims 2-3, 5-21, 26-30, 37, 118-120, and 122-125 will be pending upon entry of the present amendment.

Claims 5, 30 and 37 have been amended to recite particular amino acids at the AA^4 position. Support for this amendment can be found, for example, in the specification as originally filed at least on page 18, lines 24-29. Claim 17 has been amended to correct dependency. Claim 19 have been amended to delete references to neutral stabilizing groups. Support for new claim 125 can be found, for example, in the specification as originally filed at least on page 18, lines 5-17 and on page 22, lines 6-29. No new matter has been added.

The specification has been amended to comply with the rules for sequence disclosure, 37 C.F.R. §§ 1.821-1.825.

The foregoing amendments and claim cancellations should in no way be construed as an acquiescence to any of the Examiner's objections and/or rejections, and have been made solely to expedite prosecution of the present application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application.

Sequence Compliance

The Examiner objects to the specification because two of the disclosed sequences are not associated with SEQ ID NO's. Accordingly, Applicants have amended the specification and the sequence listing to include the missing SEQ ID NO's.

Rejection of Claims 19 and 121 under 35 U.S.C. § 112, second paragraph

Claims 19 and 121 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claim 121 has been canceled, thus rendering its rejection moot.

Claim 19 is objected to for reciting stabilizing groups which are not negatively charged. Accordingly, claim 19 has been amended to delete reference to stabilizing groups with one carboxylate group, e.g., pyroglutamic acid, acetic acid, gluconic acid, 1- and 2-naphthylcarboxylic acids, polyethylene glycolic acid, and carboxyphenyl boronic acid, which would not be negatively charged at physiological pH.

Claim 19 is also objected to as containing additional species which "do not *per se* have a negative charge, except under specific conditions which favor deprotonation of the

free carboxylate (or sulfonate)." Applicants note, however, that the stabilizing groups recited in amended claim 19 do include a negative charge at physiological pH, and submit that one of ordinary skill in the art would clearly appreciate this.

Accordingly, Applicants respectfully request that this rejection of the claims under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejection of Claims 4-8, 11, 13-17, 19, 25, 26, 30 and 118 under 35 U.S.C. § 103(a)

Claims 4-8, 11, 13-17, 19, 25, 26, 30 and 118 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Trouet *et al.* (5,962,216), in view of Veronese (U.S. Patent No. 5,286,637), Dalborg (U.S. Patent No. 6,048,720), Gaetner *et al.* (*Bioconj. Chem.* (1996) 7(1), pages 38-44), and Inada *et al.* (*Methods Enzymol.* (1994) 242, pages 65-90). Applicants respectfully traverse this rejection.

The rejected claims are directed to compounds comprising: (1) a therapeutic agent capable of entering a target cell, (2) an oligopeptide of the formula $(AA)_n$-AA^4-AA^3-AA^2-AA^1, and (3) a negatively charged stabilizing group, and (4) optionally, a linker group not cleavable by TOP. Applicants note that polyethylene glycolic acid has been deleted from claim 19.

The primary reference, Trouet *et al.*, fails to teach or suggest any prodrug conjugate comprising a negatively charged stabilizing group, as presently claimed by Applicants. The secondary references, Veronese, Dalborg, Gaertner, and Inada, each fail to overcome this deficiency. In fact, each of these references teach the use of PEG, a neutral stabilizing group. None of the cited references, alone or in combination, teach or suggest the use of a negatively charged stabilizing group.

Therefore, Applicants respectfully request that this rejection of the claims under 35 U.S.C. § 103(a) be withdrawn.

Rejection of Claims 2, 3, 5-8, 11, 13-19, 23-26, 28-30, 37, 118, 119, 120 and 122-124 under 35 U.S.C. § 103(a)

Claims 2, 3, 5-8, 11, 13-19, 23-26, 28-30, 37, 118, 119, 120 and 120-124 have been rejected under 35 U.S.C. § 103 (a) as being unpatentable over Trouet *et al.* (WO 96/05863) or Trouet *et al.* (U.S. Patent No. 5,962,216) (collectively hereinafter referred to as "Trouet *et al.*"), each in view of Li *et al.* (*J. Biol. Chem.* (1990) 235, 2638-2641), DeJongh *et al.* (*Biomed. Mass Spec.* (1976) 3, 191-195), Kartre (U.S. 4,931,544), Kilbanov (U.S. 4,414,147), Holcenberg *et al.* (*J. Biol. Chem.* (1975), 250 (11) 4165-4170), Hall (U.S. 4,144,333), Guthiel (U.S. 5,574,107), or LaRochelle (U.S. 5,833,986), as set forth at pages 5-11 of the Office Action dated April 5, 2006 (attached as Appendix

D). In particular, the Examiner asserts that succinylation of the positively charged prodrug, βAla-Leu-Ala-Leu-Dox, taught by Trouet *et al.*, would have been obvious in view of the secondary references which teach succinylation for the purposes of (1) increasing the half life of proteins (Li *et al.* and Holcenberg *et al.*), (2) to protect amino groups (Gutheil and Hall), (3) increasing the solubility of proteins (Li *et al.* and Kartre), (4) decreasing the hydrophobicity of proteins (Kilbanov), and (5) to aid in analysis using mass spectrometry of peptide fragments (DeJongh *et al.*).

Applicants respectfully disagree and traverse this rejection. Each of the aforementioned purposes for succinylating proteins taught by the secondary references does not apply to the prodrugs including βAla-Leu-Ala-Leu-Dox, taught by the primary reference, Trouet *et al.*, for at least the following reasons. Therefore, the combination of references cited by the Examiner does not establish a *prima facie* case of obviousness.

(1) One of ordinary skill in the art would not have been motivated to succinylate the βAla-Leu-Ala-Leu-Dox prodrug described by Trouet *et al.* to increase the prodrug's half-life, because Trouet *et al.* explicitly teach that the prodrugs "remain stable in the serum and in the blood, and [are] insensitive to the action of the circulating proteinases and peptidases associated with the red cells" (see e.g., U.S.5,962,216, col. 8, lines 41-44). Moreover, although both Holcenberg *et al.* and Li *et al.* describe the use of succinylation to decrease the amount of degradation of proteins *in vivo*, one of ordinary skill in the art would not have been motivated to combine the teachings of Trouet *et al.* with these secondary references, because the prodrugs taught by Trouet *et al.* were specifically designed to be stable in whole blood and selectively cleaved in the vicinity of particular target cells. Further, one of ordinary skill in the art would not have been motivated to have used succinyl as described by Li *et al.* and Holcenberg *et al.*, because they may have reasonably inferred that succinylation would affect the ability of the prodrugs taught by Trouet *et al.* to be cleaved by the target cell enzymes.

(2) One of ordinary skill in the art would not have been motivated to succinylate the prodrugs taught by Trouet *et al.* to increase their stability by protecting amino groups within the prodrug, as described by Gutheil and Hall, because there was no indication in the prior art in that the prodrugs taught by Trouet *et al.* were unstable in the first place. In fact, Trouet *et al.* teaches away from the need to protect the amino group of the presently claimed prodrugs by teaching that the compounds are already stable in blood and serum (U.S.5,962,216, col. 8, lines 41-44). Therefore, one of ordinary skill in the art would not have been motivated to modify the Trouet *et al.* prodrugs in any manner to improve their stability, let alone by adding a negatively charged stabilizing group, such as succinyl.

(3) One of ordinary skill in the art would not have been motivated to succinylate the prodrugs taught by Trouet *et al.* to increase their solubility, as taught by Li *et al.* and Kartre, because Trouet *et al.* taught that the prodrugs were already water soluble (see, Example 11 of U.S. 5,962,216). Indeed, the teachings of Li *et al.* and Kartre are directed to increasing the solubility of large insoluble proteins, not small prodrugs, such as those presently claimed.

(4) One of ordinary skill in the art would not have been motivated to succinylate the prodrugs taught by Trouet *et al.* to decrease their hydrophobicity, as described by Kilbanov, because Kilbanov teaches decreasing the hydrophobicity of interferons by attaching succinyl groups to carbohydrates associated with the interferons. It would have been clear to one of ordinary skill in the art that the prodrugs taught by Trouet *et al.* are substantially structurally different, and do not comprise associated carbohydrates as taught by Kilbanov. Therefore, one of ordinary skill in the art would not have been motivated to succinylate the Trouet prodrugs based on the teachings of Kilbanov, because the Trouet prodrugs do not comprise associated carbohydrates and are structurally very different from the compounds described by Kilbanov.

(5) One of ordinary skill in the art would not have been motivated to succinylate the prodrugs taught by Trouet *et al.* to aid in mass spectrometric analysis, as described by DeJongh *et al.*, because DeJongh *et al.* used succinylated protein fragments to increase the number of ions in the high mass regions to aid in sequence identification of unknown peptide fragments. In contrast to the peptide fragments described in DeJongh *et al.*, the Trouet prodrugs comprise a therapeutic agent. The therapeutic agent significantly increases the molecular weight of the protein, making the use of succinyl or other groups to increase the number of fragments in the high mass regions unnecessary. Furthermore, since the Trouet prodrugs utilize specific known sequences of amino acids, an ordinarily skilled artisan would not have been motivated to succinylate the Trouet prodrugs as taught by DeJongh *et al.* because the sequence of the prodrug was already known in the prior art.

In contrast to the teachings of the prior art, the above-referenced patent application teaches that the non-succinylated prodrug compounds of the present invention are acutely toxic, and that incorporation of a negatively charged stabilizing group, such as succinyl, substantially reduces this problem. In particular, Applicants observed that non-succinylated βAla-Leu-Ala-Leu-Dox is extremely toxic to mice *in vivo*. For example, Applicants performed studies in which five mice were administered (intravenously) non-succinylated βAla-Leu-Ala-Leu-Dox at a dose of 174 μMol/ml. In these studies all five

mice died immediately, as described in Example 23 on pages 64-65 and in Table 12 under "Control (i.v.)" of the present application,

In an effort to overcome this problem, Applicants tested whether the positive charge of the prodrug attributed to its toxicity. Applicants first did this by co-administering the prodrug with heparin (an agent that masks the positive charge of βAla-Leu-Ala-Leu-Dox), and unexpectedly observed that the toxicity was substantially reduced (see, Table 12, page 65 of the present application).

Applicants next tried producing the same reduced toxicity by adding a negatively charged stabilizing group, e.g., succinyl, to the prodrug. Specifically, in Example 23 on page 65 of the present specification, Applicants showed that capping the terminal amino group of βAla-Leu-Ala-Leu-Dox with a negatively charged moiety results in the complete disappearance of the acute toxicity at dose levels as high as 250 mg Dox-HCl, eq./kg. In this experiment, all mice survived up to eight days when intravenously administered the succinylated prodrug of the invention. This result was unexpected and significant because when a lower dose of the non-succinylated prodrug was administered to the mice, all of the mice died immediately. Indeed, acute toxicity of the prodrugs was not recognized in the prior art, let alone a solution taught or suggested.

For at least the above reasons, the use of negatively charged stabilizing groups, such as succinyl, in the prodrugs of the presently claimed invention would not have been obvious over the prior art.

For at least the foregoing reasons, Applicants respectfully request that this rejection of claims 2, 3, 5-8, 11, 13-19, 23-26, 28-30, 37, 118, 119, 120 and 122-124 under 35 U.S.C. § 103(a) be withdrawn.

Rejection of Claims 2, 3, 5-8, 11, 13-19, 23-26, 28-30, 37, 118, 119, 120, and 122-124 under Judicially Created Doctrine of Obviousness Type Double Patenting

Claims 2, 3, 5-8, 11, 13-19, 23-26, 28-30, 37, 118, 119, 120 and 122-124 are rejected under the judicially created doctrine of nonstatutory obviousness-type double patenting as being unpatentable over Trouet *et al.* (U.S. 5,962,216), in view of Li *et al.* (*J. Biol. Chem.* (1990) 235, 2638-2641), DeJongh *et al.* (*Biomed. Mass Spec.* (1976) 3, 191-195), Kartre (U.S. 4,931,544), Kilbanov (U.S. 4,414,147), Holcenberg *et al.* (*J. Biol. Chem.* (1975), 250 (11) 4165-4170), Hall (U.S. 4,144,333), Gutheil (U.S. 5,574,107), or LaRochelle (U.S. 5,833,986).

For at least the reasons described above, the presently claimed invention is not obvious over the claims of Trouet *et al.* (U.S. 5,962,216) alone or in combination with the cited references. Accordingly, Applicants respectfully request that the rejection of claims

2, 3, 5-8, 11, 13-19, 23-26, 28-30, 37, 118, 119, 120, and 122-124 under the judicially created doctrine of obviousness type double patenting be withdrawn.

Provisional Rejection of Claims 2, 3, 5-12, 14, 15, 17-19, 21, 23-27, 30, 37, and 122-124 under Judicially Created Doctrine of Obviousness Type Double Patenting

Claims 2, 3, 5-12, 14, 15, 17-19, 21, 23-27, 30, 37, and 122-124 are provisionally rejected under the judicially created doctrine of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-8, 11, 13-18, 23-29, 57, 58, 60, 61 and 63 of Pickford *et al.* (U.S.S.N. 10/311,411). Applicants note that the instant application and Pickford *et al.* are commonly owned and were commonly owned at the time of invention of Pickford *et al.*

While in no way admitting that claims 2, 3, 5-12, 14, 15, 17-19, 21, 23-27, 30, 37, and 122-124 are obvious over claims 1, 4-8, 11, 13-18, 23-29, 57, 58, 60, 61 and 63 of U.S.S.N. 10/311,411. Applicants will consider submitting a terminal disclaimer in compliance with 37 C.F.R. §1.321(b) and (c), if appropriate, if and when both applications are allowed.

Rejection of Claims 2, 3, 5-8, 11, 14-16, 18, 19, 23-26, 30, 37, and 122-123 under 35 U.S.C. § 102 (e)

Claims 2, 3, 5-8, 11, 14-16, 18, 19, 23-26, 30, 37, and 122-123 are rejected under 35 U.S.C. § 102 (e) as being anticipated by Garsky (U.S. Patent No. 5,948,750).

Applicants respectfully traverse this rejection. The rejected claims are directed to compounds comprising: (1) a therapeutic agent capable of entering a target cell, (2) an oligopeptide of the formula $(AA)_n$-AA^4-AA^3-AA^2-AA^1, and (3) a negatively charged stabilizing group, and (4) optionally, a linker group not cleavable by TOP, wherein AA^4 is selected from the group consisting of β-alanine, thiazolidine-4-carboxylic acid, 2-thienylalanine, 2-naphthylalanine, D-alanine, D-leucine, D-methionine, D-phenylalanine, 3-amino-3-phenylpropionic acid, γ-aminobutyric acid, 3-amino-4,4-diphenylbutyric acid, tetrahydroisoquinoline-3-carboxylic acid, 4-aminomethylbenzoic acid, and aminoisobutyric acid.

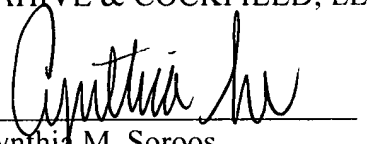
Garsky *et al.* teach conjugates useful for the treatment of prostate cancer, such as Suc-Hyp-Ala-Ser-Chg-Gln-Ser-Leu-Dox. Garsky *et al.* do not teach or suggest conjugates of Applicants formula, wherein AA^4 is β-alanine, thiazolidine-4-carboxylic acid, 2-thienylalanine, 2-naphthylalanine, D-alanine, D-leucine, D-methionine, D-phenylalanine, 3-amino-3-phenylpropionic acid, γ-aminobutyric acid, 3-amino-4,4-diphenylbutyric acid, tetrahydroisoquinoline-3-carboxylic acid, 4-aminomethylbenzoic

acid, or aminoisobutyric acid. Therefore, Applicants respectfully request that this rejection of claims 2, 3, 5-8, 11, 14-16, 18, 19, 23-26, 30, 37, and 122-123 are rejected under 35 U.S.C. § 102 (e) be withdrawn.

SUMMARY

It is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,
LAHIVE & COCKFIELD, LLP



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